

Review

Neuromyelitis Optica Spectrum Disorder: A Clinical Review

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Abstract

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune astrocytopathy in which antibodies against the aquaporin-4 (AQP4) water channel produce a stereotyped group of syndromes determined by the anatomical distribution of AQP4 expression. Six core clinical presentations are recognized: optic neuritis, longitudinally extensive transverse myelitis, area postrema syndrome, acute brainstem syndrome, diencephalic syndrome, and cerebral syndrome. Because disability in NMOSD almost always accrues at discrete, treatable relapses rather than through insidious progression, early recognition, supported by prompt AQP4-IgG testing and pattern recognition on MRI, is essential to preserving vision, mobility, and independence. This review summarizes the pathophysiology, clinical and radiologic features, diagnostic evaluation, and differential diagnosis of each core syndrome and synthesizes contemporary evidence for relapse prevention. Over the past decade, the therapeutic landscape has been transformed: agents targeting complement (eculizumab, ravulizumab), the interleukin-6 receptor (satralizumab, tocilizumab), and B cells (rituximab, inebilizumab) now have randomized evidence of efficacy in seropositive disease, with complement inhibitors ranking highest across indirect treatment comparisons. Evidence in seronegative disease remains limited, no approved agents have been compared head-to-head, and the optimal role of early plasma exchange is unsettled. Emerging neuroprotective strategies and chimeric antigen receptor T-cell therapy, both of which remain experimental, may further expand options for refractory disease. Once uniformly disabling, AQP4-IgG NMOSD is now a highly treatable condition in which timely diagnosis and sustained immunotherapy can meaningfully alter long-term outcomes.

Keywords: neuromyelitis optica spectrum disorder; aquaporin-4 IgG antibody; optic neuritis; longitudinally extensive transverse myelitis; area postrema syndrome; immunotherapy



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1. Introduction

Aquaporin-4 (AQP4) is an integral membrane water channel expressed on many cell types, including in the lung, kidney, muscle, gastrointestinal tract, and, most relevant clinically, throughout the central nervous system [1]. It is located chiefly on astrocytic end-feet that abut endothelial cells, forming part of the blood–brain barrier [1]. These channels also assemble into higher-order structures called orthogonal arrays of particles (OAPs), which enhance antibody binding and activate complement [1]. Antibodies directed against AQP4 are directly pathogenic and are detectable in over 80% of patients with neuromyelitis optica spectrum disorder (NMOSD), the principal disease these antibodies produce [1,2]. Nonetheless, NMOSD may still be diagnosed clinically in the absence of these antibodies [2].

NMOSD comprises six core clinical syndromes: optic neuritis, longitudinally extensive transverse myelitis, area postrema syndrome, acute brainstem syndrome, diencephalic syndrome, and cerebral syndrome [2]. This review addresses each of these core manifestations in detail, as they relate to antibodies directed against AQP4 channels, and we will discuss existing and emerging therapies for this disorder. Where consensus guidance is cited, it refers to the revised recommendations of the Neuromyelitis Optica Study Group, published in two parts covering diagnosis and differential diagnosis, and attack therapy and long-term management [3,4]. The 2015 international consensus diagnostic criteria are summarized in Table 1.

Table 1. NMOSD Diagnostic Criteria for Adult Patients [2].

Component	Requirement
Core clinical characteristics	(1) Optic neuritis; (2) acute myelitis; (3) area postrema syndrome (unexplained hiccups, nausea, or vomiting); (4) acute brainstem syndrome; (5) symptomatic narcolepsy or acute diencephalic syndrome with typical MRI; (6) symptomatic cerebral syndrome with typical MRI
With AQP4-IgG	≥1 core characteristic + positive AQP4-IgG (cell-based assay preferred) + exclusion of alternative diagnoses
Without/unknown AQP4-IgG	≥2 core characteristics from ≥1 attack, meeting all of: (a) ≥1 is optic neuritis, LETM, or area postrema syndrome; (b) dissemination in space (≥2 different core characteristics); (c) MRI requirements met. AQP4-IgG must be negative or unavailable, with exclusion of alternatives
MRI requirements (seronegative/unknown)	Optic neuritis: optic nerve T2-hyperintense or gadolinium-enhancing lesion over >½ the nerve length or involving the chiasm. Myelitis: LETM ≥ 3 segments, or ≥3-segment focal atrophy. Area postrema: dorsal medulla lesion. Brainstem: periependymal lesion

AQP4-IgG-positive NMOSD is a single, mechanistically defined disease, an antibody-mediated astrocytopathy in which a pathogenic IgG1 autoantibody binds AQP4 on astrocytic end-feet and triggers complement-dependent astrocyte injury. Patients who satisfy the 2015 clinical criteria without AQP4-IgG do not constitute an equivalent entity. AQP4-IgG-negative NMOSD is a heterogeneous and provisional category encompassing assay-negative AQP4 autoimmunity, unrecognized alternative diagnoses, and disorders that remain unclassified, whose members share a syndromic definition rather than a common mechanism [3]. Throughout this review, accordingly, NMOSD denotes AQP4-IgG-positive disease unless stated otherwise; wherever the data derive from mixed or seronegative populations, this is identified explicitly in the text.

2. Literature Search Methodology

We searched PubMed from January 2004, the year in which AQP4-IgG was identified, to June 2026. Search terms paired the disease with each core syndrome and with the main diagnostic and therapeutic topics: “longitudinally extensive transverse myelitis”, “area postrema syndrome NMOSD”, “brainstem syndrome NMOSD”, “diencephalic syndrome NMOSD”, “narcolepsy NMOSD”, “cerebral syndrome NMOSD”, “aquaporin-4”, “cell-based assay”, “eculizumab NMOSD”, “ravulizumab NMOSD”, “satralizumab NMOSD”, “tocilizumab NMOSD”, “rituximab NMOSD”, and “inebilizumab NMOSD”. The reference lists of retrieved articles were hand-searched for additional sources.

Eligible sources were peer-reviewed, English-language publications reporting original human data or consensus recommendations relevant to the epidemiology, clinical features, imaging, diagnosis, differential diagnosis, or treatment of NMOSD. Randomized

controlled trials, prospective cohorts, international consensus criteria, and large multicenter or population-based series were prioritized. Case reports and small series were retained only where they illustrate rare but clinically instructive presentations. Non-English publications and preclinical studies without direct clinical correlation were excluded. Where sources conflicted, precedence was given to the larger, more recent, and methodologically stronger study.

3. Clinical Syndromes of AQP4-IgG NMOSD

3.1. Optic Neuritis

AQP4-associated optic neuritis is among the most severe of the inflammatory optic neuropathies, characterized by a posterior and chiasmal predilection, bilaterality in about a fifth of patients upon presentation, and poor recovery. This severity reflects the dense AQP4 expression of the anterior visual pathway on optic nerve and chiasmal astrocytes, which makes it a preferential target for injury mediated by antibody and complement. The demographics show an approximately 9:1 female predominance, a mean onset near 40 years, and a higher prevalence in patients of Asian or African descent [5]. Optic neuritis is the isolated presenting event in roughly 31.5% of patients [6], and more than 85% of adults present with optic neuritis or myelitis [1]. Age and ancestry both matter: younger onset is associated with recurrent optic neuritis and blindness, and in a multicenter study of 441 patients, both younger age and African ancestry were independent risk factors for blindness, the latter among the strongest demographic predictors of severe visual loss [5].

Acute features: The usual triad is periocular pain worsened by eye movement, dyschromatopsia, and visual loss. Pain is common, exceeding 80% across NMOSD, but there are no characteristic pain features that distinguish it from other causes of optic neuritis [5,7]. Color vision deserves particular attention: it is characteristically and disproportionately impaired, often before the patient appreciates the full extent of acuity loss, and it tends to recover more slowly than high-contrast acuity [5]. A relative afferent pupillary defect is expected in unilateral disease but may be absent when involvement is bilateral or sequential, and the two eyes are affected symmetrically [5].

Acuity and visual fields: At nadir, more than 80% of eyes reach $\leq 20/200$; roughly 30% remain $\leq 20/200$ after a single event, rising to 70% in relapsing disease. More than 40% of untreated seropositive patients are blind in one or both eyes by 5 years and at least 60% by 10 years after onset [1,5,8]. Visual fields are also informative: central scotomas appear in only 53% of episodes, while the remainder show non-central patterns, particularly altitudinal defects, which the 2015 criteria flag as suggestive of NMOSD [2,9]. Merle and colleagues characterized automated fields in NMO eyes both in the absence of optic neuritis and after a single episode. Among eyes that had sustained one episode of optic neuritis, 40% showed diffuse loss of the entire field, 21% showed broad neurologic defects such as hemianopia or quadrantanopia, and 27% showed fascicular nerve fiber bundle defects, 12% of them altitudinal. Notably, total field loss after a single episode carried a 92.8% positive predictive value for NMO, making it a useful early discriminator from other optic neuropathies [10].

Laterality: Bilateral simultaneous optic neuritis occurs in about 20% of cases. Most initial events are unilateral, but recurrence is common, with roughly 55% experiencing a second event within 1 year and 78% within 3 years in relapsing disease without contemporary treatment [2,5,8].

Fundus and OCT: Disc edema appears in only 10–44% of cases, a consequence of the retrobulbar predominance [5,11]. When atrophy develops, it is often diffuse, spread across all peripapillary sectors [12,13]. The retinal nerve fiber (RNFL) loss can be severe: even after a single episode, 88% of eyes have a peripapillary RNFL below 60 μm , with the most affected

eyes approaching $\sim 35\text{--}50\text{ }\mu\text{m}$, close to an anatomical floor below which little measurable axonal tissue remains [14,15]. Average macular RNFL measures $33.91 \pm 8.90\text{ }\mu\text{m}$ and ganglion cell-inner plexiform layer (GCIPL) thickness $54.89 \pm 11.06\text{ }\mu\text{m}$, against 38.88 and $64.42\text{ }\mu\text{m}$ in healthy controls [16]. The structure–function relationship is non-linear. A “hockey stick” model places an inflection near a peripapillary RNFL and GCIP of $60\text{ }\mu\text{m}$. Below that threshold, each additional micron of thinning may produce disproportionately more visual function loss [17]. Neuroaxonal loss is greatest after the first attack, and even between relapses the retina continues to thin more than healthy controls, at roughly $0.66\text{ }\mu\text{m}$ per year in RNFL and $0.25\text{ }\mu\text{m}$ per year in GCIPL; GCIPL loss also appears in fellow eyes without optic neuritis, driven by contralateral disease, implying subclinical or trans-synaptic degeneration [14,18].

MRI: The signature lesion is a longitudinally extensive one in the optic nerve, with posterior and chiasmal predilection, frequent bilaterality, and acute enhancement [5,19,20] (Figure 1). Adequate assessment requires dedicated orbital MRI, with fat-suppressed T2/STIR and post-gadolinium T1 and thin coronal sections through the nerves and chiasm, alongside brain and cord imaging [13]. A lesion exceeding half the nerve length, or involving the chiasm, carries diagnostic weight when the patient is seronegative [2].

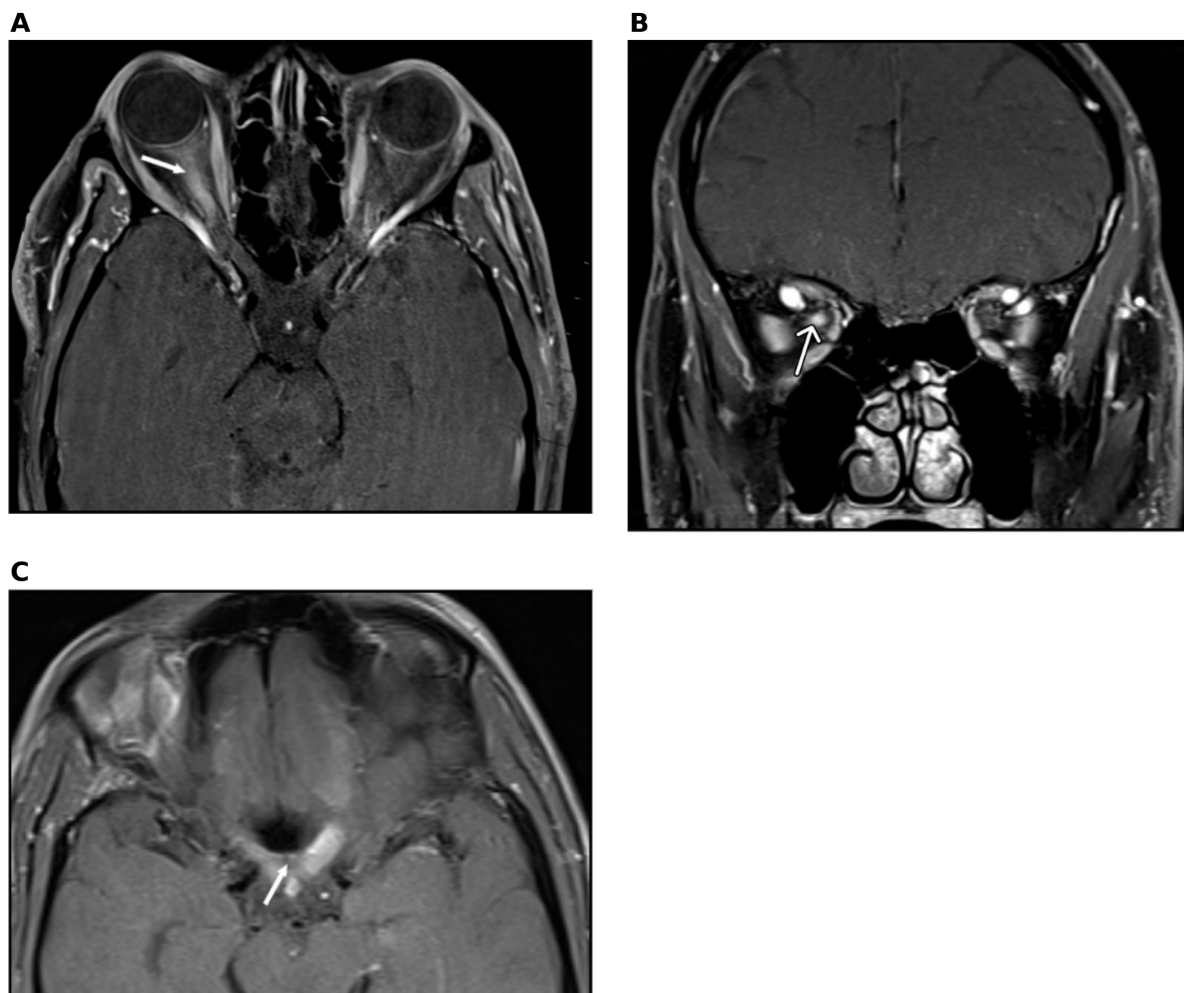


Figure 1. Optic neuritis and chiasmitis in AQP4-IgG NMOSD. (A) Axial and (B) coronal fat-saturated, post-contrast T1-weighted MRI of the orbits, from the same patient, demonstrate longitudinally extensive enhancement of the right optic nerve (arrow). (C) Axial post-contrast T1-weighted MRI, from a different patient, demonstrates enhancement of the optic chiasm, evidence of chiasmitis (arrow).

Temporal dynamics: Retinal injury progresses rapidly after acute injury. Ganglion cell-inner plexiform layer thinning proceeds at roughly 2.17–2.38 μm per week over the first 45 days before slowing to about 0.22 μm per month, while peripapillary RNFL loss moves through an initial rapid phase across the first ~45 days and a slower phase afterward, with most measurable RNFL loss accruing within three to six months of the attack [5,21]. The implication is practical: the window in which acute intervention can still preserve tissue is narrow [21].

Prognosis: Because disability is accrued attack by attack, the corollary is an encouraging one: prompt acute treatment, paired with early preventive therapy, provides the greatest opportunity to preserve vision [5,6]. The visual prognosis here is among the most guarded of the inflammatory optic neuropathies; although visual recovery appears to be meaningfully better when treatment is delivered early and escalated without delay. Acute attack management, including the indications for and timing of plasma exchange, is addressed together for all core syndromes in Section 6.1.

3.2. *Longitudinally Extensive Transverse Myelitis*

Frequency: Myelitis is one of the two commonest manifestations of NMOSD, presenting initially in roughly 42% of a United Kingdom seropositive cohort and occurring in about 66% over the disease course in a Chinese series. Initial LETM also signals a worse prognosis, with a median time to EDSS ≥ 4 of 4 years versus 13 years for other NMOSD phenotypes [22,23].

Clinical features: The myelitis of NMOSD is characteristically complete rather than partial and can suggest the diagnosis [2]. Motor loss tends to be severe, with a nadir EDSS of 6.5 ± 2.0 , producing para- or quadriplegia according to the level of the lesion, a discrete sensory level, and early bladder and bowel dysfunction in most episodes [24,25]. Paroxysmal tonic spasms, brief 15–60 s episodes of painful agonist–antagonist co-contraction, often mistaken for seizures and frequently appearing during recovery, are particularly suggestive of NMOSD [23]. Lhermitte phenomenon and pruritus occur as well, and a high cervical attack may extend into the medulla and threaten the respiratory centers, producing neurogenic respiratory failure, a leading contributor to mortality [1,26].

MRI: The lesion is a T2-hyperintensity spanning ≥ 3 segments, with central gray-matter predominance extending into white matter, cervical and upper-thoracic predilection, T1 hypointensity that tracks severity, bright spotty lesions, patchy enhancement persisting up to 20 days, and frequent brainstem extension [19,27–29] (Figure 2). Bright spotty lesions are very hyperintense, sharply demarcated intramedullary foci on axial T2-weighted images, brighter than the surrounding cerebrospinal fluid and typically transient during the acute phase. They were described initially as a feature separating the myelitis of NMOSD from that of multiple sclerosis [30], and in a later acute-myelitis cohort they were observed in 30% of AQP4-IgG-positive patients [31]. Their presence therefore argues for AQP4-IgG-positive disease, although their absence does not exclude it. Cross-sectional extent is similarly informative, and involvement of more than two-thirds of the cord area on axial imaging is characteristic of AQP4-IgG-positive myelitis. Two caveats temper the assumption that all lesions are long: 14% of initial episodes are short, under 3 segments, though 92% of these become extensive on later attacks [32], and non-LETM lesions appear on 50% of cervical studies [29]. Lesions rarely resolve fully, shrinking by 60–80% in size but leaving residual scar [33].

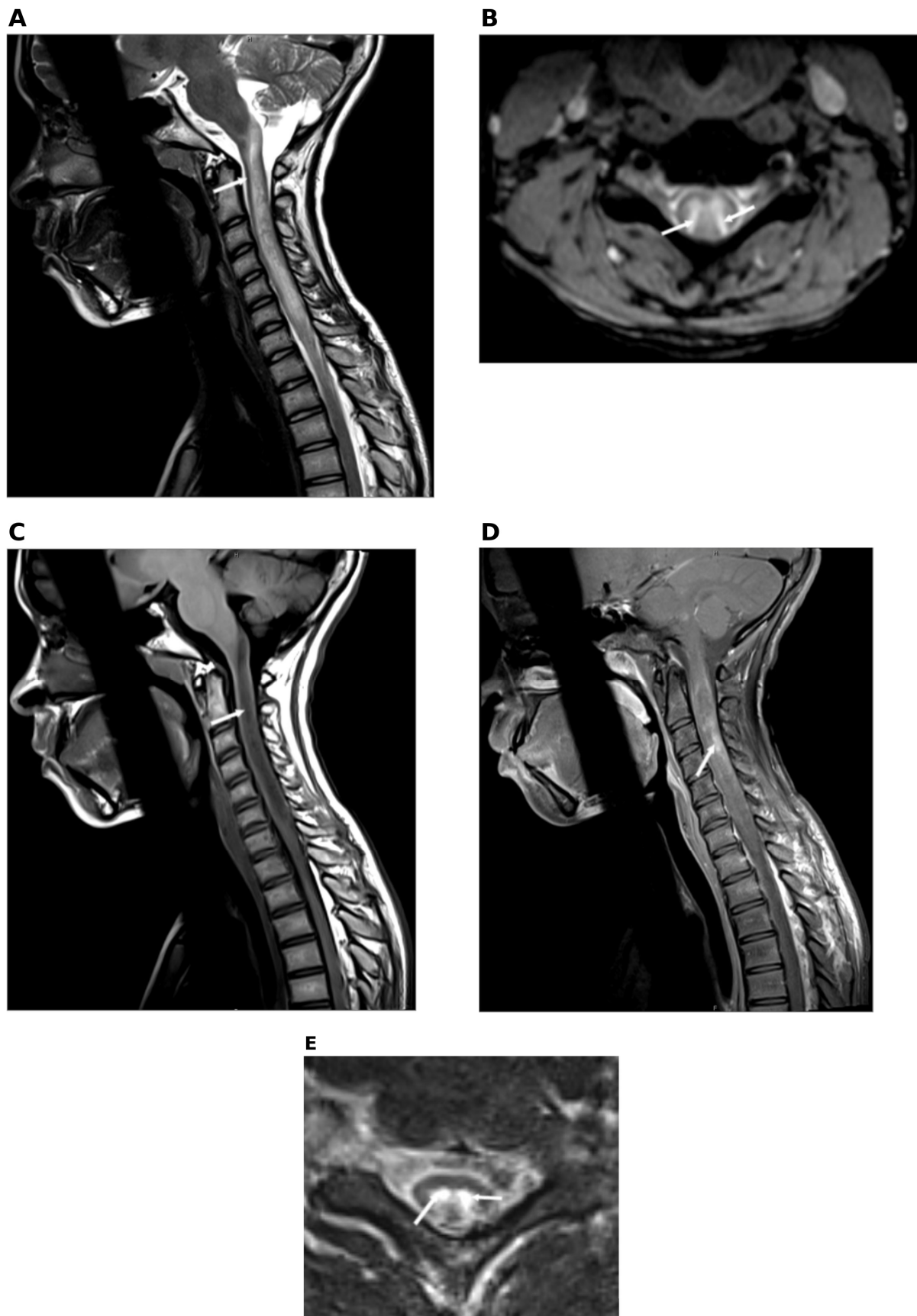


Figure 2. Longitudinally extensive transverse myelitis in AQP4-IgG NMOSD. (A) Sagittal T2-weighted image demonstrates a longitudinally extensive, centrally predominant cord lesion of T2 hyperintensity

extending over more than three contiguous vertebral segments. **(B)** Axial T2-weighted image through the cervical cord shows gray-matter-predominant T2 hyperintensity involving more than two-thirds of the cord cross-sectional area, the axial correlate of the longitudinally extensive lesion. Cross-sectional involvement of this degree favors AQP4-IgG-positive myelitis. **(C)** Sagittal pre-contrast T1-weighted image shows corresponding longitudinally extensive T1 hypointensity; co-localizing T1 hypointensity within the lesion indicates severe parenchymal destruction—necrosis, cavitation, and astrocytic and glial loss—and is a marker of attack severity and poorer recovery. **(D)** Sagittal post-contrast T1-weighted image reveals patchy enhancement along the T2-hyperintense segment, reflecting active inflammation with blood–brain barrier breakdown. **(E)** Axial T2-weighted image of a different patient at the level of the lesion demonstrates bright spotty lesions, discrete, markedly hyperintense intramedullary foci, a finding that favors AQP4-IgG-positive myelitis. Arrows indicate the abnormalities described.

Atrophy: Focal cord atrophy maps onto lesion sites, chiefly in the upper cervical (C2–C4) and upper thoracic (T1–T3) cord, and is absent in patients with no visible lesions [34]. Serum glial fibrillary acidic protein and neurofilament light chain rise with faster atrophy, whereas rituximab, encouragingly, is associated with slower progression [35]. Cerebrospinal fluid findings are considered with the overall diagnostic work-up in Section 4.2.

Outcomes: Disability is relapse-dependent and accrues in a stepwise fashion; secondary progressive courses are rare. The untreated natural history is sobering. Roughly half of untreated patients reach EDSS 3.0 by 10 months and EDSS 6.0 by 46 months, and 88% and 71%, respectively, cross those thresholds within 10 years. Among patients with recurrent LETM, 36% require a cane within 5 years, and mortality approaches 10% by that point [36,37]. These figures describe the untreated course, however, and that distinction matters: because nearly all of this disability is incurred at discrete, treatable attacks rather than through silent progression, effective acute treatment and relapse prevention can substantially alter the trajectory. Acute management is addressed in Section 6.1.

3.3. Area Postrema Syndrome

Pathophysiology: The area postrema is an AQP4-rich circumventricular emetic center. Its lesions show AQP4 loss and inflammation but, notably, no demyelination or necrosis, which is the basis for its near-universal recovery [38].

Frequency and heralding: The syndrome is the presenting feature in 7–10% of patients and occurs in 16–43% over the disease course [2,38]; it frequently serves as a herald, preceding a typical attack in 68% of cases, with that attack being myelitis in 44% and optic neuritis in 16% [38].

Presentation and MRI: The syndrome is defined by intractable nausea, vomiting, or hiccups occurring with a dorsal medullary lesion. In the largest phenotypic series, nausea was present in 81% of episodes (median 14 days), vomiting in 72% (a median of five episodes per day), and hiccups in 65%, with all three present simultaneously in roughly 45% and isolated area postrema syndrome accounting for 32–50% of episodes [38,39]. There is a diagnostic trap here: because an isolated first presentation may mimic a primary gastrointestinal illness, these patients are usually evaluated by internists or gastroenterologists for intractable vomiting, and the diagnosis is often delayed until other neurologic symptoms appear, a pattern especially common in children, in whom several gastrointestinal diagnoses are entertained before NMOSD is reached [1,40]. The corresponding lesion is distinctive: a linear T2/FLAIR signal in the dorsal medulla adjacent to the fourth ventricle, often contiguous with cervical myelitis and occasionally MRI-occult, among the most specific imaging findings in NMOSD and it is part of the seronegative MRI criterion [1,2,41] (Figure 3). Shosha and colleagues proposed formal diagnostic criteria and a severity scale adapted from the Pregnancy-Unique Quantification of Emesis (PUQE) score, a validated

three-item instrument grading nausea duration, vomiting frequency, and retching over the preceding 24 h, to which their adaptation adds hiccup severity by duration (Table 2); 80% of patients met criteria for severe disease at nadir [38,42].

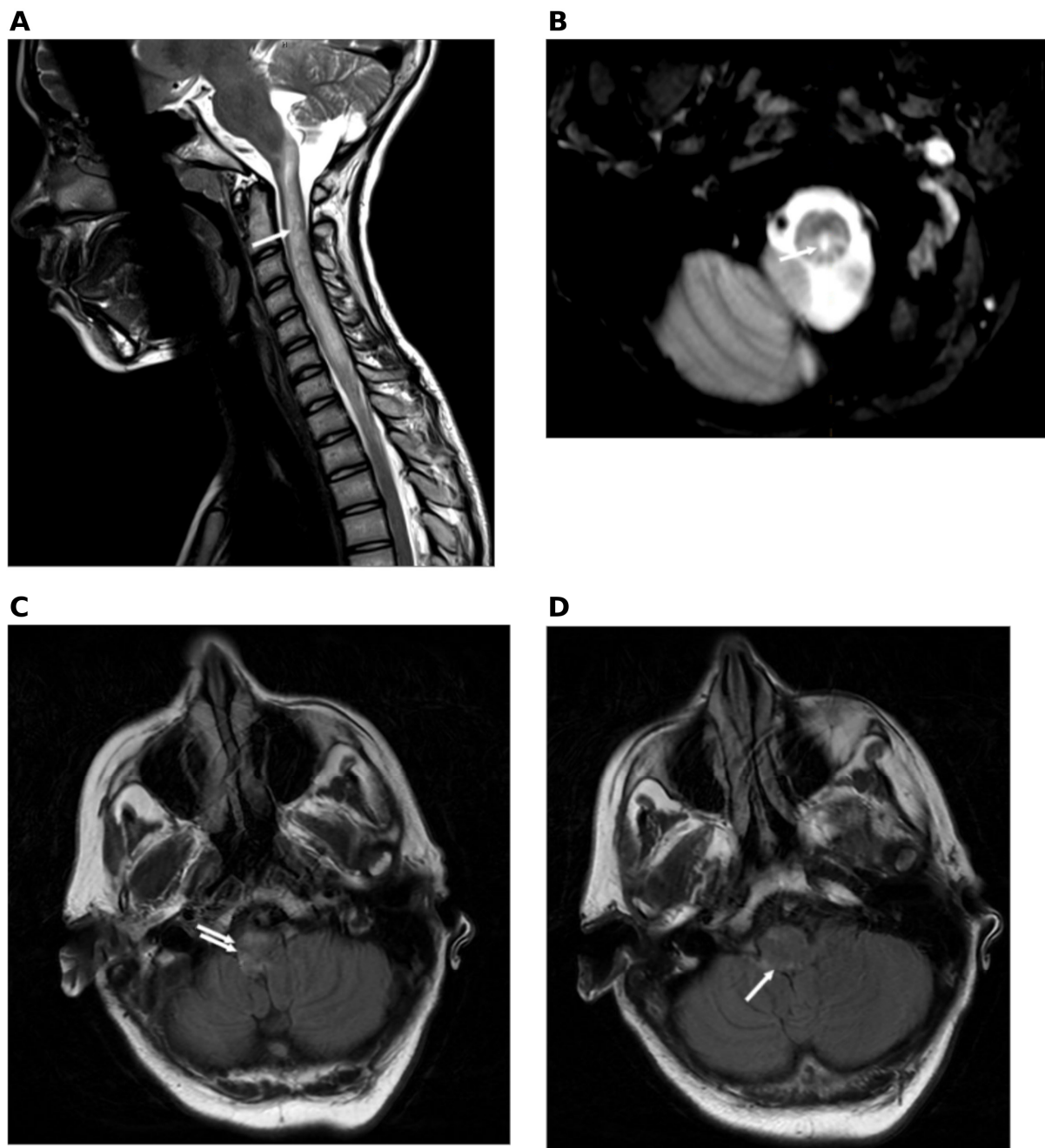


Figure 3. Area postrema syndrome. (A) Sagittal and (B) axial T2-weighted images from the patient shown in Figure 2 demonstrate rostral extension of the cervical cord lesion to the dorsal medulla, with linear dorsal medullary T2 hyperintensity adjacent to the fourth ventricle that underlies the syndrome. (C,D) Axial T2-FLAIR images from a different patient show medullary hyperintensity that is dorsal and also extends ventrally. The area postrema is an AQP4-rich circumventricular emetic center in the dorsal medulla, and its involvement accounts for the intractable nausea, vomiting, and hiccups that define the syndrome. Arrows indicate the abnormalities described.

Table 2. Area Postrema Syndrome Severity Grading [38], Based on the Modified PUQE Score.

Item (Preceding 24 h)	1 Point	2	3	4	5
Nausea (duration)	None	≤1 h	2–3 h	4–6 h	>6 h
Vomiting (episodes)	0	1–2	3–4	5–6	≥7
Retching (episodes)	0	1–2	3–4	5–6	≥7
Total score 3–15: mild ≤ 6; moderate 7–12; severe ≥ 13. The area postrema adaptation additionally grades hiccup severity by symptom duration.					

Outcome and associations: The prognosis is encouraging: 95% of episodes resolve completely with immunotherapy, whereas antiemetics alone fail in roughly 75%, and, unlike optic neuritis or myelitis, isolated area postrema attacks leave no measurable residual disability on the EDSS [6,38]. In a large Latin American cohort, 18.3% of patients developed the syndrome during follow-up, and relapse activity tended to decline in the year after its onset [39]. The syndrome is distinguished from gastrointestinal causes by the combination of antiemetic refractoriness, the dorsal medullary lesion, AQP4-IgG seropositivity, and a rapid response to immunotherapy.

3.4. Acute Brainstem Syndrome

This fourth core characteristic requires periependymal brainstem lesions [2]. Brainstem onset occurs in about 20% of patients, including area postrema-type symptoms. Brainstem lesions are the second most common brain finding after hemispheric lesions; the medulla is most often affected, and involvement is more frequent in seropositive than seronegative disease [29,43,44]. The clinical presentation spans cranial-nerve and long-tract signs, including diplopia, vertigo, facial hypoesthesia, nystagmus, dysarthria, dysphagia, ataxia, and internuclear ophthalmoplegia or sixth-nerve palsy, often with intractable nausea, vomiting, or hiccups [1,43]. Misdiagnosis in this group is common, reaching 46%, and is more likely with older onset or when the patient first presents to a non-neurology service, such as otolaryngology for vertigo or gastroenterology for vomiting; vestibular disorders, posterior-fossa stroke, and multiple sclerosis are common alternative labels [43]. On MRI, the most specific finding is a dorsal medullary lesion adjacent to the fourth ventricle, often contiguous with the cervical cord; lesions may extend rostrally into the pons and periaqueductal gray matter, cerebellar lesions appear in roughly 14% of patients, and enhancement is patchy and cloud-like, with both DWI and ADC hyperintense, in keeping with vasogenic rather than cytotoxic edema [19,44]. The annual relapse rate exceeds that of other initial manifestations; like other relapses confined to the brain rather than the optic nerve or spinal cord, an isolated brainstem attack leaves no measurable EDSS disability, though extensive medullary or high cervical involvement can be life-threatening through neurogenic respiratory failure [6,43].

3.5. Diencephalic Syndrome and Symptomatic Narcolepsy

The fifth core characteristic involves the AQP4-rich diencephalon, including the thalamus, hypothalamus, and the structures surrounding the third ventricle and cerebral aqueduct. Antibody-mediated inflammation here disrupts the hypothalamic–pituitary axis, orexin and hypocretin-producing neurons, and the centers that regulate temperature and osmolality [2,19,45,46]. Symptomatic disease is uncommon, and most diencephalic lesions seen on MRI are clinically silent [19,47]. When it does occur, symptomatic narcolepsy presents as acute, severe hypersomnia with up to 16 h of daily sleep and sudden sleep attacks, typically without cataplexy, hypnagogic hallucinations, or sleep paralysis; despite the absence of cataplexy, CSF hypocretin is low, and multiple sleep latency testing shows

a short mean latency with sleep-onset REM periods, fulfilling narcolepsy criteria [46]. A polysomnographic study of 26 patients found shorter sleep latency and a higher frequency of hypersomnia and narcolepsy than controls, along with an increased apnea-hypopnea index [48]. Other manifestations include hypothalamic endocrinopathies (hypothyroidism, hyperprolactinemia, secondary amenorrhea or galactorrhea, obesity, and eating disturbance), autonomic dysfunction (hypothermia, hypotension, and arrhythmia), the syndrome of inappropriate antidiuretic hormone secretion, and behavioral or cognitive change [1,19]. Cardiovascular and osmoregulatory involvement are readily missed and deserve particular emphasis. Autonomic cardiovascular control may be disturbed, including rare recurrent syncope from sick-sinus dysfunction that resolves with immunotherapy and may spare the patient a pacemaker [41]. Sodium and water balance may also be disrupted. In one hyponatremia cohort, 16% of patients met criteria for the syndrome of inappropriate antidiuretic hormone secretion and 12% presented with it as their first NMOSD attack [49]. Because these manifestations reflect hypothalamic and adjacent circumventricular involvement rather than area postrema pathology, they should prompt dedicated diencephalic imaging even when the presenting complaint is nausea or vomiting. MRI shows periependymal T2/FLAIR lesions circumscribing the third ventricle and involving the thalamus, hypothalamus, and anterior border of the midbrain, occasionally bilaterally hypothalamic [19,50]. The response to treatment is encouraging: immunotherapy usually resolves the hypersomnolence and normalizes hypocretin, distinguishing the disorder from idiopathic type 1 narcolepsy, in which hypocretin-neuron loss is permanent; established endocrinopathies, however, may require ongoing hormonal replacement [46].

3.6. Cerebral Syndrome

The sixth core characteristic spans hemispheric white-matter, callosal, periventricular, and corticospinal-tract lesions [2]. Brain abnormalities, once thought rare, are now identified in 51–89% of seropositive patients and in 82.5% of the PAMRINO cohort, with roughly 60% of patients accumulating asymptomatic white-matter lesions over time and as many as 16% fulfilling the Barkhof criteria used to define dissemination in space in multiple sclerosis; even so, a symptomatic cerebral syndrome remains uncommon in adults, while affecting 45–55% of children [2,19,29,47]. When symptoms do appear, they include encephalopathy, hemiparesis, hemianopia, aphasia, cognitive decline, and ataxia, and in children the picture may closely mimic acute disseminated encephalomyelitis, which makes AQP4 testing essential [1,51]. Seizures are rare in seropositive disease, occurring in approximately 1% of patients [52]. Several MRI patterns are characteristic and worth recognizing. Periependymal lesions follow the ependymal lining rather than projecting perpendicularly like the Dawson fingers of multiple sclerosis. Callosal lesions, present in 12–40% of patients, hug the ventricles and run along the long axis of the corpus callosum; acutely they appear edematous and heterogeneous (a “marbled” pattern), and they occasionally span the full thickness of the splenium in an “arch-bridge” configuration. Extensive or tumefactive hemispheric lesions are usually without mass effect and show increased diffusivity, indicating vasogenic edema. Longitudinally extensive corticospinal-tract lesions run from the deep white matter through the posterior limb of the internal capsule to the cerebral peduncles and pons in 23–44% of cohorts, notable because the corticospinal tracts are not regions of high AQP4 expression. Enhancement is typically patchy and cloud-like [19,20,26,53,54]. Tumefactive lesions occur in approximately 5% of seropositive patients; large lesions typically reduce in size by 60–80% over time but rarely resolve completely, and may cavitate [33,55]. Volumetric studies demonstrate significant reductions in total brain, gray-matter, and white-matter volume, with notable atrophy of the accumbens, brainstem, caudate, cerebellum, hippocampus, putamen, and thalamus;

thalamic atrophy is the most prominent deep-gray-matter finding and correlates with EDSS and cognition, while hippocampal volume independently predicts cognitive performance [56–58]. Cognitive impairment affects roughly 25% of children and, in adults, tracks thalamic and hippocampal volume rather than white-matter lesion burden [58,59]. Representative imaging of the brainstem, diencephalic, and cerebral syndromes is shown in Figure 4.

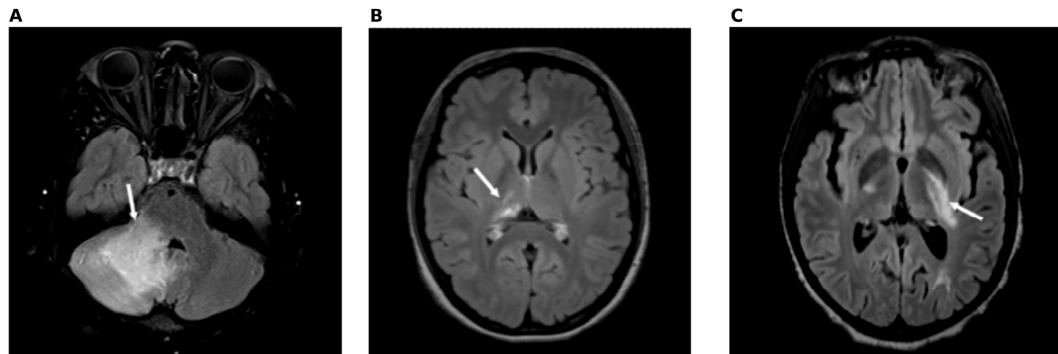


Figure 4. Representative imaging of the remaining core syndromes of AQP4-IgG NMOSD. (A) Acute brainstem syndrome: axial FLAIR image demonstrates an infiltrative, expansile hyperintense lesion centered in the right cerebellar hemisphere and extending into the right middle cerebellar peduncle (brachium pontis) and vermis, with mass effect partially effacing the fourth ventricle; the lesion showed minimal diffusion restriction and nodular parenchymal and leptomeningeal enhancement. (B) Diencephalic syndrome: axial FLAIR image demonstrates hyperintensity in the right thalamus. (C) Cerebral syndrome: axial FLAIR image demonstrates hyperintensity involving the posterior limbs of both internal capsules, asymmetrically and more extensively on the left, which also showed restricted diffusion. Arrows indicate the abnormalities described.

4. Diagnostic Evaluation

The diagnosis of NMOSD rests on three elements: a compatible core clinical syndrome, a reliable antibody result, and the exclusion of alternative causes. The first has been addressed above; the second is considered here and the third in Section 5.

4.1. Serologic Testing for AQP4-IgG

Serum is the preferred specimen. AQP4-IgG is produced peripherally and is present at substantially higher titer in serum than in cerebrospinal fluid; testing cerebrospinal fluid adds little when the serum is positive, is rarely positive when the serum is negative, and a negative cerebrospinal fluid result should therefore never be used to exclude the diagnosis [3].

Assay choice matters more than is often appreciated. In a multicenter comparison of AQP4-IgG assays, cell-based methods outperformed enzyme-linked immunosorbent and tissue-based assays, both of which are more prone to false-negative results at low titer and to false-positive results near the cut-off [60]. Live cell-based assays, in which AQP4 is expressed in its native conformation on unfixed cells, are the most sensitive format and detect a proportion of patients missed by fixed commercial assays. A fixed cell-based assay remains acceptable for routine practice, but a negative fixed assay in a patient whose phenotype is strongly suggestive should be repeated on a live assay at a reference laboratory before that patient is designated seronegative [3].

Timing and concurrent treatment affect the result. Titers can fall with corticosteroid treatment, plasma exchange, and B-cell depletion, so serum should ideally be drawn before these are given; when that is not possible, a negative result obtained during or shortly after acute immunotherapy should be repeated once the patient is stable [3]. Results

near the manufacturer's cut-off, and results discordant with the clinical picture, warrant confirmation on a cell-based assay rather than acceptance at face value. One interpretive principle is easily forgotten: the positive predictive value of any assay falls as pretest probability falls, so a low-positive result in a patient whose phenotype is atypical for NMOSD is more likely to be false-positive than to indicate disease [3,60]. Conversely, a clear-positive cell-based result in a patient with a compatible syndrome is sufficient for diagnosis with a single core clinical characteristic [2]. Where AQP4-IgG is negative, and the phenotype nonetheless remains compatible, the next step is not to accept a diagnosis of seronegative NMOSD but to work through the differential, as set out in Section 5.

4.2. Cerebrospinal Fluid

Cerebrospinal fluid analysis does not establish the diagnosis, but helps support it, helps exclude mimics, and should be part of the initial work-up in any suspected case rather than reserved for patients presenting with myelitis. The profile differs markedly from that of multiple sclerosis. Oligoclonal bands are found in fewer than 20% of patients and, when present, are often transient; one dedicated cohort reported only 10.5% positivity, associated there with higher cell counts and more frequent early relapses [26,61]. Acute attacks commonly show a pleocytosis above 50 cells/ μ L, sometimes neutrophilic or eosinophilic, a pattern distinctly unusual in multiple sclerosis; cerebrospinal fluid protein and neurofilament light chain run substantially higher than in multiple sclerosis, reflecting the greater tissue destruction of each attack [26,62]. A markedly inflammatory profile of this kind also mandates exclusion of infection before immunotherapy is escalated (Section 5).

5. Differential Diagnosis

The 2015 criteria require exclusion of alternative diagnoses, and the cost of failing to do so runs in both directions. Interferon beta, natalizumab, and fingolimod may aggravate NMOSD, while mislabeling an infectious, vascular, or compressive myelopathy as NMOSD delays treatment that is time-critical [2,3,63]. The problem is most acute in the AQP4-IgG-negative patient, in whom the diagnosis rests entirely on phenotype and exclusion of other diagnostic considerations. This section sets out the principal alternatives for each core syndrome; the discriminating features are discussed below.

Multiple sclerosis: Multiple sclerosis is both the commonest misdiagnosis and the most consequential. Optic neuritis in multiple sclerosis is typically unilateral, mid-orbital, and short-segment, with good spontaneous recovery; myelitis is partial, spans fewer than two vertebral segments, and is dorsolaterally rather than centrally placed. Brain lesions are ovoid and oriented perpendicular to the ventricles (Dawson fingers), with juxtacortical and infratentorial involvement, whereas NMOSD lesions follow the ependymal lining. Cerebrospinal fluid remains the most useful single discriminator. Oligoclonal bands are present in more than 85% of patients with multiple sclerosis and in fewer than 20% of those with NMOSD, and a pleocytosis above 50 cells/ μ L is distinctly unusual in multiple sclerosis [2,3,26,53].

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD): MOGAD overlaps clinically with NMOSD but is a separate entity. MOGAD-associated optic neuritis is more often bilateral, anterior with prominent disc edema, painful, and markedly steroid-responsive, with better visual recovery; perineural enhancement extending into orbital fat is characteristic. Myelitis frequently involves the conus, may show the H-sign (T2 hyperintensity confined to central gray matter in an H-shaped configuration), and can be short-segment, while bright spotty lesions are essentially absent [28,30,31,64]. Attacks resolve more completely, and MRI lesions often disappear entirely, in contrast to the residual scar left by AQP4-IgG-positive disease [33]. MOG-IgG on a cell-based assay settles the

distinction and should be sent in any AQP4-IgG-negative patient who would otherwise be labeled as having seronegative NMOSD [64].

Acute disseminated encephalomyelitis: Acute disseminated encephalomyelitis presents with encephalopathy and multifocal deficits, usually in children and often after infection or vaccination, with large, poorly demarcated, bilateral hemispheric and deep gray lesions and a typically monophasic course. The overlap is greatest in pediatric NMOSD, in which a cerebral syndrome may be indistinguishable at onset; because MOGAD accounts for a substantial share of pediatric acquired demyelination, both AQP4-IgG and MOG-IgG should be tested [51,59,64].

Idiopathic and parainfectious transverse myelitis: A longitudinally extensive cord lesion is not synonymous with NMOSD. In series of patients labeled as having idiopathic transverse myelitis, systematic re-evaluation identifies a specific alternative diagnosis in a substantial proportion, and antibody testing reclassifies a further group as AQP4-IgG- or MOG-IgG-positive [3,63]. Parainfectious myelitis follows a recognized systemic infection, is usually monophasic, and lacks both the relapsing course and the antibody signature of NMOSD. Where no antibody is found, and the lesion is short, dorsolateral, or non-enhancing, the diagnosis should remain provisional, prompting repeat imaging and repeat serology rather than commitment to lifelong immunotherapy.

Infectious myelitis: Infection must be excluded before immunotherapy is escalated, particularly when the cerebrospinal fluid is markedly inflammatory or neutrophilic. Varicella zoster virus, herpes simplex virus, enteroviruses, human T-lymphotropic virus type 1, human immunodeficiency virus, syphilis, tuberculosis and, in endemic regions, schistosomiasis can all produce longitudinally extensive myelitis. Fever, meningism, a very high cell count, hypoglycorrhachia, and a relevant exposure or travel history are the practical discriminators, and targeted serology and polymerase chain reaction testing should be sent at presentation [3,63].

Non-demyelinating mimics: Several non-inflammatory disorders reproduce the NMOSD phenotype and are systematically under-recognized [63]. Spinal cord infarction is abrupt, maximal within hours, and typically anterior, with diffusion restriction and sometimes adjacent vertebral body infarction. Spinal dural arteriovenous fistula produces a progressive longitudinally extensive lesion with prominent perimedullary flow voids. Neurosarcoidosis characteristically shows dorsal subpial and leptomeningeal enhancement. Systemic lupus erythematosus and Sjögren syndrome coexist with AQP4-IgG-positive NMOSD more often than they mimic it, so a positive antinuclear or anti-Ro antibody does not exclude the diagnosis and should prompt AQP4-IgG testing rather than replace it. Glial fibrillary acidic protein astrocytopathy produces a linear radial periventricular enhancement pattern. Paraneoplastic myelopathy, most often associated with anti-Hu, CRMP5/anti-CV2, or amphiphysin antibodies, intramedullary neoplasm, and nutritional myelopathy from vitamin B12 or copper deficiency complete the list. Vascular, compressive, and metabolic causes should be excluded on imaging and laboratory testing before an inflammatory label is applied [3,63].

The same principles hold across all six core syndromes. A longitudinally extensive or bilateral lesion is suggestive but not specific. A negative fixed cell-based assay does not settle the question. And a diagnosis of seronegative NMOSD should be made only once MOGAD, infection, vascular and compressive causes, and systemic inflammatory disease have been excluded; even then it should be revisited whenever the course diverges from expectation [3,63].

6. Treatment

6.1. Management of Acute Relapses

The principles of acute attack management are the same for every core syndrome and are therefore set out once here rather than repeated within each. Because disability in NMOSD accrues almost entirely at attacks, speed matters more than the choice of agent.

High-dose intravenous methylprednisolone, conventionally 1 g daily for 3 to 5 days, is first-line and should be started as soon as an attack is recognized [4]. Infection can rarely be excluded outright at presentation, and waiting for certainty costs time that the optic nerve and cord do not have. What is required in practice is that no clear source of infection has been identified, that initial screening is unremarkable, and that the probability of an active infection driving the presentation is judged low. Where suspicion is higher, as with fever, meningism, a markedly or neutrophilically inflammatory cerebrospinal fluid, or hypoglycorrhachia, cultures and targeted testing should be sent and empirical antimicrobial therapy started alongside corticosteroids rather than in place of them. An oral taper is commonly used to bridge to preventive therapy and to reduce the risk of early rebound.

Plasma exchange is the principal escalation, and the evidence increasingly favors using it early rather than holding it in reserve. Retrospective series consistently show that outcome correlates with the interval from attack onset to exchange, with the greatest benefit when it is begun within days [4]. It is indicated for incomplete response to corticosteroids and, increasingly, concurrently with them in severe attacks. Severity is best defined pragmatically as visual acuity worse than 20/200 in the worse affected eye, or myelitis producing a functionally significant motor or sphincter deficit. Functionally significant is deliberately not tied to a fixed motor score, because the same examination finding carries different weight in different lives: a mild monoparesis that a sedentary patient would tolerate may end a career for someone whose work or sport depends on that limb, and the threshold for exchange should be set with the patient against their own baseline demands. Typical regimens comprise five to seven exchanges on alternate days; immunoadsorption is an alternative where available. The timing question is being addressed prospectively in TIMELY-PLEX, which randomizes patients to early versus rescue plasma exchange [65]; the trial enrolls acute inflammatory myelitis and optic neuritis generally rather than NMOSD specifically, so its result will need to be applied to the AQP4-IgG-positive population with that in mind.

Intravenous immunoglobulin is a reasonable third-line option when plasma exchange is unavailable or contraindicated, although the supporting evidence is weaker. What to do when an attack fails to stabilize depends on how the patient has responded to what has already been given. Where there has been partial improvement, a further cycle of exchange or a second course of corticosteroids is reasonable. Where there has been little or no response to both adequate corticosteroids and adequate plasma exchange, repeating either is unlikely to change the trajectory and delays definitive treatment; the more useful steps are to confirm the diagnosis, look again for an alternative or superimposed process, and move promptly to preventive immunotherapy rather than to continue cycling rescue treatments.

Serum for AQP4-IgG should be drawn before plasma exchange and, where possible, before corticosteroids, since both lower the titer (Section 4.1). Preventive immunotherapy should be started as soon as the diagnosis is secure rather than deferred until recovery from the index attack is complete, because the risk of a second attack is highest during the first year [4].

A relapse occurring on established preventive therapy raises a different question. The first step is to confirm that a true attack has occurred, since infection, fever, and metabolic stress can unmask a fixed deficit convincingly enough to be mistaken for one, and a new lesion on MRI is the most reliable corroboration. The second is to establish that the drug

was actually delivered and biologically active, which for anti-CD20 and anti-CD19 agents means checking B-cell reconstitution and, for the others, checking adherence and infusion intervals. A breakthrough attack on a repopulated B-cell compartment calls for tighter redosing rather than a change in drug. A breakthrough attack on demonstrably adequate therapy is harder to justify treating with more of the same, and the usual step is to switch mechanism, most often from B-cell depletion to complement inhibition or IL-6 receptor blockade, since these act on different points of the pathway and complement inhibition takes effect within days [4]. No trial has compared switching strategies directly, and the sequence remains a matter of judgment.

6.2. Relapse Prevention: Comparative Evidence

The treatment of NMOSD has advanced remarkably quickly: in little more than a decade, the disease has moved from having no approved therapy to a substantial menu of agents with proven efficacy in relapse prevention. Comparative efficacy was evaluated in a Bayesian network meta-analysis [66], pooling eight randomized controlled trials and 851 patients, 716 of them (84%) seropositive. The primary endpoint was time to first relapse. Annualized relapse rate (ARR) was also used as a common endpoint. ARR was the pre-specified primary endpoint in only one trial [67] and used as a secondary measure in the other seven.

Treatment rankings were derived using the Surface Under the Cumulative Ranking Curve (SUCRA), a probability-based measure of how likely a given therapy is to outperform all others in the network simultaneously. Values range from 0 to 1, where 1.0 represents the highest probability of superiority. One caveat is worth keeping in mind: SUCRA reflects relative standing within the network rather than the absolute magnitude of the treatment effect, and should therefore be read alongside hazard ratios and their credibility intervals. Reassuringly, the rankings held steady across both the time-to-first-relapse and ARR analyses. Table 3 summarizes the contributing trials, their comparators, and the resulting rankings.

Two older oral immunosuppressants require brief mention, since neither is represented in the comparison above. Azathioprine enters the network only as the active comparator in TANGO and in the Nikoo trial, not as an evaluated intervention in its own right, and mycophenolate mofetil does not appear in it at all; the evidence for either in NMOSD is retrospective and uncontrolled. Both act more slowly and less completely than the approved biologics, and neither should be preferred where an approved agent can be obtained. They are noted here because they remain in wide use where cost or infusion access precludes the biologics, and because the reproductive, hepatic, and malignancy considerations in Section 6.7 apply to them [4].

6.3. Complement Inhibitors

Ravulizumab and eculizumab both target complement protein C5, blocking its cleavage into C5a and C5b and thereby preventing anaphylatoxin-mediated astrocyte injury and terminal complement activation, the central pathogenic mechanism in AQP4-IgG seropositive NMOSD. Acting directly on this final common pathway appears effective: complement inhibition ranked highest of all three drug classes across both primary and secondary analyses. That ranking, however, derives from indirect comparison within a network of heterogeneous trials rather than from head-to-head evidence, and should be read accordingly.

Table 3. Summary Comparison of Immunotherapies for NMOSD Relapse Prevention.

Drug	N (tx)	N (ctrl)	Comparator	Follow-Up (mo)	Relapses tx/ctrl	SUCRA
Complement inhibitors						
Ravulizumab	58	External	External placebo	27.7	0/20	0.99
Eculizumab	96	47	Placebo	48.7	3/20	0.69
IL-6 receptor antagonists						
Tocilizumab	59	59	AZA	13.8	8/28	0.47
Satralizumab	63/41	32/42	Placebo	18.0/24.8	19/16 · 8/18	0.32
B-cell depleting agents						
Rituximab	19/40	19/46	Placebo/AZA	16.6/12.0	0/7	0.48
Inebilizumab	174	56	Placebo	6.5	21/22	0.44

SUCRA, Surface Under the Cumulative Ranking Curve; AZA, azathioprine; tx, treatment; ctrl, control. Relapse counts shown as treatment/control; the satralizumab and rituximab columns combine two trials where applicable. All data in this table are drawn from the Bayesian network meta-analysis of John et al. [66]; the contributing trials are CHAMPION-NMOSD [68] (ravulizumab), PREVENT [69] (eculizumab), TANGO [70] (tocilizumab), SAKuraStar [71] and SAKuraSky [72] (satralizumab), RIN-1 [73] (rituximab), and N-MOMentum [74] (inebilizumab). SUCRA values express relative rank within the network and are not treatment-effect estimates; no head-to-head randomized comparison exists between any two of these agents, and the trials differ in comparator, follow-up duration, seropositivity rate, and relapse definition. Enrolment and relapse events here are for the full randomized populations, which in several trials included AQP4-IgG-seronegative patients; the seropositive-subgroup figures are given in the text. Where an agent was evaluated in two trials, values are given for each in the order named: satralizumab in SAKuraStar then SAKuraSky, and rituximab in RIN-1 then the Nikoo trial. Ravulizumab had no concurrent control; the 20 control relapses shown are those of the PREVENT placebo arm, used as a pre-specified external comparator. The relapse counts shown for rituximab are those of RIN-1, the Nikoo trial having not reported counts in a form the network could use.

6.3.1. Ravulizumab

Ravulizumab ranked first overall (ARR-based SUCRA 0.99) and first in the seropositive subgroup (SUCRA 0.92), the strongest performance of any agent in the network. In CHAMPION-NMOSD [68], all 58 enrolled patients were seropositive and remained entirely relapse-free over 27.7 months, a striking result. The trial used the placebo arm of PREVENT as a pre-specified external control, as eculizumab's prior approval precluded a concurrent placebo arm. Ravulizumab ranked above every other intervention in both the overall and seropositive analyses, although the comparison is indirect and the control arm was external rather than concurrent, so residual differences between the two trial populations cannot be excluded [66].

Most treatment-emergent adverse events were mild or moderate and unrelated to ravulizumab, and no deaths occurred during the primary treatment period. Two vaccinated patients developed meningococcal infection; both recovered without sequelae and one continued treatment. The meningococcal risk is real but manageable: mandatory pre-treatment vaccination and routine vigilance for invasive disease keep it in check [68].

6.3.2. Eculizumab

Eculizumab ranked second overall (SUCRA 0.69) and third in the seropositive subgroup (SUCRA 0.57). In PREVENT [69], all 96 eculizumab-treated and 47 placebo-treated patients were seropositive, and the treatment arm experienced only 3 relapses against 20 on placebo over 48.7 months, the longest follow-up of any included trial and a durable demonstration of benefit [66].

The safety profile mirrors ravulizumab, consistent with the shared mechanism of terminal complement inhibition. Treatment-emergent adverse events were reported in most patients in both arms of PREVENT, 92% on eculizumab and 96% on placebo. That figure counts any event arising during a median exposure approaching two years, irrespective

of attribution, and does not indicate a drug poorly tolerated: the commonest events were upper respiratory tract infection (29% versus 13% on placebo), headache (23% versus 23%), nasopharyngitis (21% versus 19%), and nausea (17% versus 26%), of which only upper respiratory infection was clearly more frequent on active treatment. Because the eculizumab arm accrued 173 patient-years against 53 in the placebo arm, PREVENT reported serious adverse events as exposure-adjusted rates rather than as proportions, and these too favored treatment: 27 versus 55 per 100 patient-years, excluding relapses. The risk that matters clinically is therefore not general toxicity but the susceptibility to *Neisseria meningitidis* that follows directly from terminal complement blockade. No meningococcal infections occurred under mandatory vaccination. There was one death in the eculizumab arm, from pulmonary empyema. Liver enzyme monitoring and vigilance for encapsulated-organism infections are now well-established components of ongoing care [69].

6.4. IL-6 Receptor Antagonists

Tocilizumab and satralizumab both target the IL-6 receptor. Their trial populations differed substantially in seropositivity, however, which likely accounts for much of the divergence in their network rankings.

6.4.1. Tocilizumab

Tocilizumab ranked third overall (SUCRA 0.47) and fourth in the seropositive subgroup (SUCRA 0.37). In TANGO [70], in which 90% of patients were seropositive, the tocilizumab arm recorded 8 relapses versus 28 on azathioprine across the full randomized population of 59 patients per group over 13.8 months, a clear advantage even against an active comparator. One caveat applies: azathioprine was the comparator, with concomitant immunosuppression permitted until week 24, so tocilizumab's relative benefit may be modestly overstated [66].

Treatment-associated adverse events occurred in 36 of 59 tocilizumab-treated patients (61%) in TANGO, fewer than the 49 of 59 on azathioprine (83%). Urinary tract infection, upper respiratory infection, and mild liver enzyme elevation were the commonest events in both arms, each more frequent on azathioprine. Serious adverse events in the tocilizumab arm included severe pneumonia, herpes zoster, deep vein thrombosis, cerebral hemorrhage, and myelitis. One death occurred in each group, neither of them considered treatment-related. With liver enzyme surveillance and attention to infection risk when it is combined with other immunosuppressants, the profile is well characterized and manageable [70].

6.4.2. Satralizumab

Satralizumab ranked sixth overall and sixth in the seropositive subgroup (SUCRA 0.32 in both). It was evaluated in two placebo-controlled trials, SAKURA-STAR [71] (63 vs. 32 patients) and SAKURA-SKY [72] (41 vs. 42 patients), and reduced relapses in both. Within the AQP4-IgG-seropositive subgroups, relapses occurred in 9 of 41 satralizumab-treated versus 13 of 23 placebo-treated patients in SAKURA-STAR, and in 3 of 27 versus 12 of 28 in SAKURA-SKY; the corresponding counts for the full randomized populations, which included seronegative patients, are given in Table 3 [66].

The most common adverse reactions ($\geq 15\%$) were nasopharyngitis, headache, upper respiratory infection, gastritis, rash, arthralgia, extremity pain, fatigue, and nausea. Reassuringly, rates of serious adverse events and infections did not differ significantly from placebo across the SAKURA trials, and long-term extension data out to seven years showed no new safety signals and no rise in infection rates over time. It also offers a practical advantage in its subcutaneous administration, which extends effective therapy to settings where infusion infrastructure is limited [71,72].

6.5. B-Cell Depleting Agents

Rituximab and inebilizumab deplete B cells through anti-CD20 and anti-CD19, respectively, with the broader CD19 target reaching plasmablasts and some plasma cells in addition to mature B cells. Both occupy the middle tier of the network overall, though rituximab's seropositive-specific performance is considerably stronger than its overall ranking suggests.

6.5.1. Rituximab

Rituximab ranked fourth overall (SUCRA 0.48) but rose to second in the seropositive subgroup (SUCRA 0.90), the largest favorable rank shift in any agent between the two analyses. In RIN-1 [73], all 19 rituximab-treated seropositive patients remained relapse-free over 16.6 months, against 7 relapses among 19 placebo-treated patients. The Nikoo trial [67] (2015–2016), comparing rituximab with azathioprine, was excluded from the seropositive subgroup analysis because it did not report seropositive-specific relapse data. One point deserves emphasis: rituximab remains a widely used and accessible off-label option in regions where the newer approved agents are not available, or the cost of other agents is too prohibitive, an important consideration for equity in global practice [66].

In the RIN-1 study, serious adverse events occurred in 16% of rituximab-treated patients. The principal considerations are familiar: infusion reactions, progressive hypogammaglobulinemia with repeated dosing, and a higher risk of serious or opportunistic infection during sustained B-cell depletion, all mitigated by hepatitis B and JC virus screening before initiation and routine monitoring thereafter. As a chimeric antibody, it carries a greater potential for anti-drug antibody formation than the fully humanized agents [73].

6.5.2. Inebilizumab

Inebilizumab ranked fifth in both the overall and seropositive analyses (SUCRA 0.44 and 0.35, respectively). In N-MOMENTUM [74], the largest trial in the meta-analysis, 161 of 174 inebilizumab-treated and 52 of 56 placebo-treated patients were AQP4-IgG-seropositive; within that subgroup, relapses occurred in 18 of 161 versus 22 of 52 over 6.5 months; that follow-up, the briefest of any included trial, tempers interpretation of the absolute difference [66].

Across 225 patients followed for up to four years in the N-MOMentum open-label extension, 92% reported at least one treatment-emergent adverse event. An open-label extension has no comparator arm, and over four years of observation almost every patient records some event, so the figure describes the duration of follow-up rather than the tolerability of the drug; the events themselves were unremarkable, most commonly urinary tract infection (26%), nasopharyngitis (21%), and arthralgia (17%). Reassuringly, infection rates did not increase over the four years, and the three deaths during the open-label phase were all judged unrelated to treatment. Given the breadth of B-lineage depletion, immunoglobulin monitoring and infection vigilance are sensible [74].

6.6. Evidence in Seronegative Disease

One important caveat underlies all of the above: the evidence base in seronegative NMOSD is far thinner than in seropositive disease, because most pivotal trials enrolled predominantly or only seropositive patients. Seronegative patients may constitute a distinct but related group of disorders compared to those that are seropositive. The complement inhibitor trials (CHAMPION-NMOSD and PREVENT) and the rituximab RIN-1 trial enrolled only seropositive patients, so neither complement inhibition nor rituximab has been formally tested in seronegative disease, and the rationale for complement inhibition is in any case strongest where AQP4-IgG is present [66]. Tocilizumab's TANGO trial was 90%

seropositive and inebilizumab's N-MOMENTUM enrolled only about 7% seronegative patients, too few in either case for separate conclusions [66].

Satralizumab is the only agent evaluated in a substantial seronegative subgroup, with seronegative patients comprising 28–35% of SAKURA enrollment; there its benefit was minimal, and its efficacy was essentially confined to seropositive disease [66]. The Nikoo trial of rituximab versus azathioprine did enroll a high proportion of seronegative patients (42–54% per arm) but did not report seropositive-specific relapse data [66]. Robust relapse-prevention evidence in seronegative NMOSD is still lacking, and treatment in these patients rests largely on extrapolation, clinical judgment, and the modest signal from satralizumab. This remains one of the clearest priorities for future trials.

Overall, all six active agents produced meaningful reductions in ARR relative to control, a uniformly positive picture across the drug class. The overall hierarchy by ARR-based SUCRA was: ravulizumab (0.99) > eculizumab (0.69) > rituximab (0.48) > tocilizumab (0.47) > inebilizumab (0.44) > satralizumab (0.32). In the seropositive subgroup, it shifted to: ravulizumab (0.92) > rituximab (0.90) > eculizumab (0.57) > tocilizumab (0.37) > inebilizumab (0.35) > satralizumab (0.32). Complement inhibitors ranked highest across all analyses, and the most notable subgroup finding was rituximab's rise to second place in seropositive patients, driven chiefly by the relapse-free RIN-1 result and the exclusion of the Nikoo trial. These orderings should be read as probabilistic ranks within a network of heterogeneous trials rather than as evidence that any one agent is superior to another; the credible intervals around most pairwise comparisons include no difference [66].

Infections are the predominant adverse-event class across all six agents, but each carries a clear and well-defined mitigation pathway: complement inhibitors require mandatory pre-treatment meningococcal vaccination, B-cell-depleting agents require hepatitis B and JC virus screening with ongoing immunoglobulin monitoring, and tocilizumab warrants liver enzyme surveillance and caution alongside other immunosuppressants. Satralizumab's subcutaneous administration and comparatively mild profile make it a convenient option where infusion access is limited.

One caveat is important. These rankings derive entirely from indirect Bayesian network comparisons; no head-to-head randomized trial yet exists between these agents, and the trials varied in follow-up (6.5–48.7 months), comparator (placebo versus azathioprine), seropositivity rate (43–100%), and relapse definitions. The hierarchy is therefore best read as population-level guidance, to be individualized considering each patient's serostatus, comorbidities, cost, tolerability, and access. A remarkable abundance of effective therapy choices has emerged for the treatment of NMOSD over the past decade. Nonetheless, newer approaches such as CAR T-cell therapy hold promise for those patients with refractory disease [66].

6.7. Choosing Among Agents in Practice

The rankings above describe average behavior across a network of trials; they do not indicate which agent to give to the patient in front of the clinician. In practice, the choice is driven less by rank order than by serostatus, comorbidity, reproductive plans, infection risk, route of administration, and access. The reasoning behind the factors that most often determine the decision is set out here.

Azathioprine and mycophenolate mofetil, noted at the end of Section 6.2, enter the discussion below only where reproductive planning, hepatic disease, malignancy risk, and access are concerned. Neither is a first choice where an approved agent can be obtained.

Serostatus is the first branch point. All six agents have randomized evidence only in AQP4-IgG-positive disease, and the mechanistic rationale for complement inhibition

applies specifically to it. In an AQP4-IgG-negative patient, the diagnosis should be revisited before therapy is escalated (Sections 4 and 5); if it holds, treatment is empirical, and B-cell depletion or an IL-6 receptor antagonist is generally preferred to complement inhibition, whose target is not demonstrably engaged in the absence of the antibody [4,66].

Pregnancy and family planning often dominate the decision in a disease with an approximately 9:1 female predominance and onset near 40 years. Relapse risk rises postpartum, so effective therapy should not simply be withdrawn on confirmation of pregnancy, and some patients cannot safely come off treatment at all. Where a change is needed, it is far better made before conception than after it. IgG crosses the placenta from the second trimester onward, and neonatal B-cell depletion has been reported after third-trimester rituximab exposure, so where B-cell depletion is continued, the dosing is best timed before conception and late-pregnancy infusions avoided. Mycophenolate mofetil is teratogenic and should be stopped, ideally at least three months before conception, with an overlapping switch to an agent that can be continued; azathioprine has the longest reproductive safety record among the older agents and is the usual destination, and the transition should be completed and tolerance confirmed before contraception is stopped rather than left to coincide with a positive test. The prior regimen can be resumed postpartum, with the timing set against breastfeeding plans and the elevated early postpartum relapse risk. These decisions belong in a joint discussion with maternal–fetal medicine [4].

Age, frailty, and infection risk pull in the same direction. Infection is the dominant adverse-event class across all six agents, and each carries a defined mitigation pathway. Complement inhibitors require meningococcal vaccination against serogroups A, C, W, Y and B, completed at least two weeks before the first dose; where treatment cannot be delayed that long, vaccination is given and antibacterial prophylaxis, usually penicillin or a macrolide in the penicillin-allergic patient, is continued for at least two weeks afterward. Vaccination does not abolish the risk, so patients should carry a safety card, and any febrile illness warrants immediate assessment and empirical broad-spectrum cover, conventionally a third-generation cephalosporin, before culture results are available. A patient who cannot be vaccinated or reliably followed is poorly suited to complement inhibition. B-cell-depleting agents require hepatitis B serology and consideration of JC virus status before initiation. Immunoglobulin levels fall cumulatively with repeated dosing and should be monitored, since a low IgG may prompt extension of the dosing interval, a change in class, or immunoglobulin replacement [4].

Hepatic disease argues against both tocilizumab and azathioprine, each of which requires transaminase surveillance. IL-6 receptor blockade also blunts the fever and C-reactive protein response that would otherwise signal infection, which matters in a frail patient.

A history of malignancy argues against prolonged lymphocyte depletion when an alternative agent exists, and against azathioprine, which carries a cumulative dose-related risk of lymphoproliferative disease and non-melanoma skin cancer. Complement inhibition and IL-6 receptor blockade do not deplete lymphocytes and are generally preferred in this setting.

Concomitant autoimmune disease may allow a single agent to serve two indications, which simplifies monitoring and reduces cumulative immunosuppression. The convenience should not be allowed to override efficacy. If one agent controls both conditions moderately while two separate agents each control their own condition well, the two-agent regimen is usually the better choice, and the clinician should resist the pull toward an elegant single answer when it costs disease control in the more dangerous of the two diseases. Given that disability in NMOSD accrues in discrete, often irreversible attacks, the NMOSD arm of that calculation should generally be optimized first, and the coexisting disease treated on its own terms unless the shared agent is genuinely competitive for both.

Route, monitoring burden, and cost decide many real-world cases. Satralizumab is subcutaneous and self-administered, which extends therapy to patients remote from infusion centers. Ravulizumab is given every eight weeks against every two weeks for eculizumab. Rituximab remains the most widely accessible agent globally and, although off-label in most jurisdictions, is often the only realistic option where the approved biologics are unaffordable—a consideration of real weight for equity in global practice.

6.8. Emerging and Experimental Therapies

The approaches described in this section are investigational. None is approved for NMOSD, none has been evaluated in a randomized controlled trial in this disease, and none should be offered outside a clinical trial or a formally supervised compassionate-use pathway.

Chimeric antigen receptor T-cell therapy: A patient's own T cells are collected, modified in the laboratory to carry a receptor directed against a chosen surface protein, and reinfused after lymphodepleting chemotherapy, after which they multiply and destroy the cells carrying that protein. The target in NMOSD is B-cell maturation antigen, which sits on plasmablasts and plasma cells. These are the cells that keep producing AQP4-IgG, and anti-CD20 and anti-CD19 drugs do not reach them.

The only published clinical experience in NMOSD is an investigator-initiated, open-label, single-arm phase 1 study of an anti-B-cell maturation antigen construct in 12 patients with AQP4-IgG-positive disease. Enrollment required continued relapses despite prior immunotherapy rather than treatment failure at the level of acute attack management alone, so the cohort had already been exposed to corticosteroids and to maintenance immunosuppression, rituximab included in most cases. Eleven of the 12 remained relapse-free over a median follow-up of 5.5 months, serum AQP4-IgG fell in most, and disability and quality-of-life measures improved. Cytokine release syndrome, the systemic inflammatory response that follows CAR T-cell activation and ranges from fever and myalgia at its mildest to hypotension, hypoxia, and organ dysfunction at its most severe, occurred in every patient but was confined to grade 1 or 2. Hematologic toxicity accounted for most grade 3 or higher events, and 58% developed an infection [75].

These were patients who had relapsed despite conventional immunosuppression, and durable remission is hard to achieve in that group by any means, so a response of this size is encouraging. It is still a phase 1 signal from 12 patients, with no comparator, short follow-up, and nothing yet on durability, secondary malignancy, or long-term immune reconstitution. Whether a single immune reset offers anything over continued biologic therapy, in a disease the approved agents already control well, remains unanswered, and the risk-benefit calculation here is not the one that applies in oncology. Controlled trials are warranted; treatment outside them is not.

Neuroprotective and remyelinating strategies: Because much of the disability from a given attack reflects irreversible astrocyte and axonal loss occurring within days, agents intended to limit that loss are of considerable interest. None has been validated in NMOSD, and the acute optic neuritis paradigm developed to test such agents in multiple sclerosis has not yet been applied at scale in this disease [21].

Other approaches: Complement inhibition at other points in the cascade, blockade of pathogenic AQP4 antibody binding by non-pathogenic competing antibodies, and antibody-lowering strategies including neonatal Fc receptor antagonists all remain preclinical or early-phase in NMOSD.

7. Remaining Challenges and Future Directions

Seronegative disease: AQP4-IgG-negative NMOSD is the largest gap in the evidence base and, arguably, in the nosology. No pivotal trial was powered for it; satralizumab is the only agent evaluated in a substantial seronegative subgroup, and there its benefit was minimal (Section 6.6). Part of the difficulty is that the category is defined by what is absent rather than by what is present. Resolving it will require more sensitive assays capable of detecting low-titer AQP4 autoimmunity that current platforms miss, identification of new antigenic targets among patients who are genuinely antibody-negative on the best available testing, and separation of those who prove to have distinct entities altogether. Until that work is done, trials in this population will remain difficult to design and to interpret, treatment will rest on extrapolation and clinical judgment, and the diagnosis itself should be reconsidered periodically [3].

Early diagnosis: Misdiagnosis remains common. Brainstem onset is misdiagnosed in nearly half of cases, area postrema syndrome is routinely attributed to primary gastrointestinal disease, and patients who present to non-neurological services are at particular risk (Sections 3.3 and 3.4). The levers here are practical rather than conceptual. Cell-based AQP4-IgG testing needs to be available with a turnaround measured in days rather than weeks, since a result that arrives after the attack has been treated no longer informs the decision it was meant to inform; intractable hiccups or vomiting without a gastrointestinal explanation, and any optic neuritis that is bilateral, posterior, or steroid-dependent, need to function as testing triggers in the services that see these patients first; and referral pathways need to allow a neurologist to be reached within days of presentation rather than at the next available clinic [43].

Relapse management: Several questions remain open here, and they are the ones clinicians actually face. When to give plasma exchange is the first, and TIMELY-PLEX is designed to answer it [65]. Distinguishing a true attack from a pseudo-relapse is the second, and it has become the harder problem now that relapses are uncommon on modern therapy; no validated biomarker exists for the distinction, and serum glial fibrillary acidic protein is the most promising candidate but is not yet ready for routine use [35]. The third concerns what to do after a confirmed breakthrough attack. Whether to intensify the current agent, switch within class, or switch mechanism has never been tested prospectively, and the sequence rests on pharmacological reasoning rather than on evidence (Section 6.1). Nor is it known how long to persist with a strategy before abandoning it, whether combination therapy has any place in patients who relapse on adequate monotherapy, or whether the poor responders represent a biologically distinct group rather than a treatment-delivery failure. Prospective switch registries and a standardized definition of treatment failure would make these questions answerable.

Long-term management and access: No trial has compared the approved agents head-to-head; none has established whether, or when, therapy can be de-escalated or withdrawn in a patient who has been relapse-free for years; and the cumulative infection and hypogammaglobulinemia risk of indefinite treatment remains incompletely characterized. Cost is the dominant barrier across much of the world, where rituximab is the only realistic option. Head-to-head trials, treatment-withdrawal studies, and pragmatic comparative-effectiveness registries would address questions that network meta-analysis, by construction, cannot [4,66].

8. Conclusions

NMOSD is best understood as an autoimmune astrocytopathy, in which an autoantibody directed against the AQP4 water channel produces a remarkably stereotyped set of syndromes, each determined by the anatomical distribution of its target. The optic nerves

and chiasm, the central gray matter of the spinal cord, and the AQP4-rich circumventricular and periependymal regions of the brainstem, diencephalon, and cerebral hemispheres are vulnerable areas. Each area of involvement may produce characteristic clinical features and distinctive imaging signatures. That coherence is itself an advantage: recognizing these patterns, together with prompt AQP4-IgG testing, allows the diagnosis to be made early. Since disability in NMOSD accrues at discrete, treatable attacks rather than through insidious progression, the disease is fundamentally actionable, and nearly every relapse is an opportunity to intervene acutely and for long-term prevention.

In seropositive disease, the position is now strong: agents targeting complement, the interleukin-6 receptor, and B cells all carry randomized evidence of benefit, and in some trials relapses were nearly abolished. Nonetheless, outcomes in seronegative patients are still being defined, no trial has compared the approved agents head-to-head, and the role of early plasma exchange alongside steroids, rather than in reserve for refractory attacks, remains unsettled. Newly initiated clinical trials will help to answer the question of when to use plasmapheresis in those patients with acute severe visual loss or transverse myelitis [65]. Likewise, neuroprotective strategies remain to be investigated, and chimeric antigen receptor T-cell therapy may eventually have a role in treatment-refractory disease. The latter should be regarded as experimental: it is supported at present by a single uncontrolled phase 1 study of 12 patients, and randomized data are not yet available [75]. For the practicing clinician, the message is both clear and hopeful: AQP4-IgG NMOSD, once a uniformly disabling disease, is now a highly treatable one, in which early recognition and sustained immunotherapy can preserve a patient's vision, mobility, and independence over the long term.

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